CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-205

MICROBIOLOGY REVIEW(S)

MICROBIOLOGY REVIEW
DIVISION OF ANTIVIRAL DRUG PRODUCTS (HFD-530)

NDA # 21, 205, Serial Number 000
Date Submitted: 12/16/99
Date Assigned: 01/28/00
Sponsor: Glaxo Wellcome Inc.
Five Moore Drive
PO Box 13398
Research Triangle Park
North Carolina 27709

Reviewer: LALJI MISHRA, Ph.D.
Date Received: 12/20/99
Date Completed : 06/02/00

Product Name(s):

Proprietary: Trizivir™
Non-proprietary: Abacavir sulfate/lamivudine/zidovudine

Route of Administration/Dosage form:Oral/Tablet

Indication: Treatment of HIV-1 infection

BACKGROUND

Glaxo Wellcome Inc. has developed Trizivir tablets and seeks marketing approval (NDA # 21,205) of Trizivir tablets for the treatment of human immunodeficiency virus (HIV-1) infection in adults. [redacted] patients. Trizivir tablets each contain abacavir sulfate, lamivudine (3TC) and zidovudine (ZDV). Abacavir, 3TC and ZDV are synthetic nucleoside analogue reverse transcriptase inhibitors (NRTIs) and each is FDA approved for the treatment of HIV-1 infection. Abacavir, 3TC and ZDV have been demonstrated to exhibit anti-HIV-1 activity both in vitro and in vivo. All supportive microbiology specific data for each compound were previously submitted to the Division for review under their respective NDAs; 20,977 (abacavir), 20,564 (lamivudine) and 19,655 (zidovudine). Therefore, the review of these previously submitted reports will not reproduced here, but can be found in the microbiology reviews of the NDA approval packages for Abacavir, 3TC and ZDV.

This NDA is based upon human bioequivalence of the Trizivir tablet to the commercially available Ziagen® tablet 300 mg, Epivir® tablet 150 mg, and Retrovir® tablet 300 mg formulations.

Proposed Microbiology Label: The following is the proposed label that can be supported by the data submitted to date.

Mechanism of Action:

Abacavir: Abacavir is a carbocyclic synthetic nucleoside analogue. Intracellularly, abacavir is converted by cellular enzymes to the active metabolite carbovir triphosphate. Carbovir triphosphate is an analogue of deoxyguanosine-5-triphosphate (dGTP). Carbovir triphosphate inhibits the activity of HIV-1 reverse transcriptase both by competing with the natural substrate dGTP and by its incorporation into viral DNA. The lack of a 3-OH group in the incorporated nucleoside analogue prevents the formation of the 5' to 3' phosphodiester linkage essential for DNA chain elongation, and therefore, the viral DNA growth is terminated.

Lamivudine: Lamivudine is a synthetic nucleoside analogue. Intracellularly, lamivudine is phosphorylated to its active 5-triphosphate metabolite, lamivudine triphosphate (L-TP). The principal mode of action of L-TP is inhibition of reverse transcriptase via DNA chain termination after incorporation of the nucleoside analogue. L-TP is a weak inhibitor of mammalian DNA polymerases α, β and mitochondrial DNA polymerase γ.

Zidovudine: Zidovudine is a synthetic nucleoside analogue. Intracellularly, zidovudine is phosphorylated to its active 5-triphosphate metabolite, zidovudine triphosphate (ZDV-TP). The principal mode of action of ZDV-TP is inhibition of reverse transcriptase via DNA chain termination after incorporation of the nucleoside analogue. ZDV-TP is a weak inhibitor of the mammalian DNA polymerase α and mitochondrial DNA polymerase γ and has been reported to be incorporated into the DNA of cells in culture.

Antiviral Activity In Vitro: The relationship between in vitro susceptibility of HIV to abacavir, lamivudine, or zidovudine and the inhibition of HIV replication in humans has not been established.

Abacavir: The in vitro anti-HIV-1 activity of abacavir was evaluated against a T-cell tropic laboratory strain HIV-1 IIIB, a monocyte/macrophage tropic laboratory strain HIV-1 BaL and clinical isolates in lymphoblastic cell lines, primary monocytes/macrophages and peripheral blood mononuclear cells, respectively. The concentration of drug necessary to inhibit viral replication by 50 percent (IC_{50}) ranged from — to — μM against HIV-1 IIIB, and was — ± — μM / μM = — mcg/mL) against 8 clinical isolates. The IC_{50} of abacavir against HIV-1 BaL varied from — to — μM. Abacavir had synergistic activity in combination with amprenavir, nevirapine, and zidovudine, and additive activity in combination with didanosine, lamivudine, stavudine, and zalcitabine in vitro. Most of these drug combinations have not been adequately studied in humans.

Lamivudine: In vitro activity of lamivudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes). IC_{50} and IC_{90} (90% inhibitory concentrations) values for lamivudine were—— mcg/mL to — mcg/mL and — to — mcg/mL, respectively. Lamivudine had anti–HIV-1 activity in all acute virus-cell infections tested.

In HIV-1–infected MT-4 cells, lamivudine in combination with zidovudine had synergistic antiretroviral activity.

Zidovudine: In vitro activity of zidovudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes). The IC_{50} and IC_{90} values for zidovudine were — to — mcg/mL and — to — mcg/mL, respectively. Zidovudine had anti-HIV-1 activity in all acute virus-cell infections tested. However, zidovudine activity was substantially less in chronically infected cell lines. In cell culture drug combination studies, zidovudine demonstrates synergistic activity with delavirdine, didanosine, indinavir, nelfinavir, nevirapine, ritonavir, saquinavir, zalcitabine, and additive activity with interferon-alpha.

Drug Resistance:

Abacavir: HIV-1 isolates with reduced sensitivity to abacavir have been selected in vitro and were also obtained from patients treated with abacavir. Genetic analysis of isolates from abacavir-treated patients showed point mutations in the reverse transcriptase gene that resulted in amino acid substitutions at positions K65R, L74V, Y115F, and M184V. Mutations M184V and L74V were most frequently observed in clinical isolates. Phenotypic analysis of HIV-1 isolates that harbor abacavir-associated mutations from 17 patients after 12 weeks of abacavir monotherapy exhibited a 3-fold decrease in susceptibility to abacavir in vitro. The clinical relevance of genotypic and phenotypic changes associated with abacavir therapy is under evaluation.

Lamivudine Plus Zidovudine Administered As Separate Formulations: In patients receiving lamivudine monotherapy or combination therapy with lamivudine plus zidovudine, HIV-1 isolates from most patients became phenotypically and genotypically resistant to lamivudine within 12 weeks. In some patients harboring zidovudine-resistant virus at baseline, phenotypic sensitivity to zidovudine was restored by 12 weeks of treatment with lamivudine and zidovudine. Combination therapy with lamivudine plus zidovudine delayed the emergence of mutations conferring resistance to zidovudine.

HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from patients after prolonged lamivudine/zidovudine therapy. Dual resistance required the presence of multiple mutations, the most essential of which may be at codon 333 (Gly→Glu). The incidence of dual resistance and the duration of combination therapy required before dual resistance occurs are unknown.

Lamivudine: Lamivudine-resistant isolates of HIV-1 have been selected in vitro and have also been recovered from patients treated with lamivudine or lamivudine plus zidovudine. Genotypic analysis of the resistant isolates showed that the resistance was due to mutations in the HIV-1 reverse transcriptase gene at codon 184 from methionine to either isoleucine or valine.

Zidovudine: HIV isolates with reduced susceptibility to zidovudine have been selected in vitro and were also recovered from patients treated with zidovudine. Genotypic analyses of the isolates showed mutations which result in 5 amino acid substitutions (M41L, D67N, K70R, K219Q, T215Y or F) in the HIV-1 reverse

transcriptase gene. In general, higher levels of resistance were associated with greater number of mutations.

Cross-Resistance: Cross-resistance among certain reverse transcriptase inhibitors has been recognized.

Abacavir: Recombinant laboratory strains of HIV-1 (HXB2) containing multiple reverse transcriptase mutations conferring abacavir resistance exhibited cross-resistance to lamivudine, didanosine, and zalcitabine in vitro.

Lamivudine: Cross-resistance between lamivudine and zidovudine has not been reported. In some patients treated with lamivudine alone or in combination with zidovudine, isolates have emerged with a mutation at codon 184 which confers resistance to lamivudine. In the presence of the 184 mutation, cross-resistance to didanosine and zalcitabine has been seen in some patients; the clinical significance is unknown. In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple drugs, including lamivudine, have emerged (see under Zidovudine below).

Zidovudine: HIV isolates with multidrug resistance to didanosine, lamivudine, stavudine, zalcitabine, and zidovudine were recovered from a small number of patients treated for ≥1 year with zidovudine plus didanosine or zidovudine plus zalcitabine. The pattern of genotypic resistant mutations with such combination therapies was different (A62V, V75I, F77L, F116Y, Q151M) from the pattern with zidovudine monotherapy, with the 151 mutation being most commonly associated with multidrug resistance. The mutation at codon 151 in combination with the mutations at 62, 75, 77, and 116 results in a virus with reduced susceptibility to didanosine, lamivudine, stavudine, zalcitabine, and zidovudine.

Multiple drug resistance has been observed in 2 of 39 (5%) patients receiving zidovudine and didanosine combination therapy for 2 years.

CONCLUSIONS

With respect to microbiology, this NDA (21,205) is supported.

RECOMMENDATIONS

Phase IV Commitment: The sponsor is requested to continue to submit data to the Division, as they become available, on viral resistance analyses from all on-going clinical trials.

/S/ 6/7/00

Microbiologist

CONCURRENCES:

HFD-530/Dep Dir — Signature 6/7/00 Date

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The current version of the Microbiology section of trizivir package insert is shown below.

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RECOMMENDATIONS

Microbiology section of trizivir package insert is supported.

/S/

Microbiologist

11/13/00